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(54) Title: AN EXTENDED RELEASE PHARMACEUTICAL COMPOSITION CONTAINING β-LACTAM ANTIBIOTICS WITH IMPROVED THERAPEUTIC EFFICACY

(57) Abstract: The invention disclosed in this application relates to an extended release oral pharmaceutical composition containing at least one β-lactam anti-biotic intended for releasing the drug over an extended period upon administration. The pharmaceutical composition is useful for maintaining the desired the therapeutic concentration of active ingredient in blood for extended time periods thus meeting the requirements for effective management of infectious diseases. The pharmaceutical composition is either in the form of a tablet, capsule or dry syrup for reconstitution at the time of administration, releasing the active ingredient as initial dose and maintenance dose at a specific rate. The invention disclosed in this application also relates to a process for formulation of an extended release pharmaceutical composition containing β-lactam antibiotics.

AN EXTENDED RELEASE PHARMACEUITCAL COMPOSITION CONTAINING β -LACTAM ANTIBIOTICS WITH IMPROVED THERAPEUTIC EFFICACY

The invention disclosed is an oral pharmaceutical composition for extended release of active ingredient, at least one β-lactam antibiotic specifically intended for the release of drugs possessing a site-specific absorption upon oral administration, useful for maintaining the desired therapeutic concentration of active ingredient in blood for an extended time periods thus meeting the requirements for effective management of certain infectious diseases minimizing the dosing frequency and patient intervention. The invention also includes a process for preparation of the pharmaceutical composition.

The oral pharmaceutical composition of the invention is a polymeric matrix containing at least one β-lactam antibiotic along with other excipients and additives, either in the form of a tablet or a capsule or a dry syrup for reconstitution at the time of administration.

The discovery of pencillins in the year 1929, by Alexander Flemming, has brought many changes in the concepts and the treatment of infectious diseases caused by bacteria and other microorganisms. Today a large number of antibiotic compounds have been developed for the treatment of infections caused by different microorganisms. Among the various types, β-lactams occupy a recognizable place. These β-lactams are active against wide variety of infections, with ideal therapeutic index, but suffers from very short biological half-life, requiring frequent administration to elicit desired therapeutic response. Further their site-specific gastrointestinal absorption may limit the therapeutic applications. Furthermore, it is well established that the contact of various β-lactams causes damage to the intestinal flora (Ref.: (a) Nord and Edlund., J. Chemother. 2,218,1990. (b) Pien FD., Antimicrobial Agents and Chemother.;24,856,1983. (c) Fleisher et al., Antimicrobial Agents and Chemother., 24,679,1983.). The poor bioavailability and adverse effects can be over come by using prodrug of the respective compounds. However prodrug approach also not yielded complete bioavailability.

A recent study (Drusano and Craig, J. Chemother., 9,38,1998) revealed that the antibiotic activity of β-lactams is solely dependent on the time of exposure to microorganisms, above its minimum inhibitory concentration (MIC) rather than the peak plasma/serum concentration. This may be obtained by continuous infusion, which may requires hospitalization and continuous monitoring.

Hence the selection of suitable alternate mode of drug administration is of primary goal since the efficacy of the drug greatly depends on the time duration above minimum inhibitory concentration (MIC). The selection should be based upon the pharmacokinetic and pharmacodynamic parameters.

In case of antibiotics the relationship between pharmacokinetic and pharmacodynamic parameters depends on three elements: the pathogen, the host and specific antimicrobial agent. The Post-antibiotic effect of the drug is another pharmacodynamic parameter that has to be considered in determining the optimal dosage regimen.

Based on the above an oral extended release preparation for β-lactam antibiotics that would maintain low but effective concentrations for a prolonged period would be the suitable mode of administration for prolonged therapy.

Arancibia et al. [Int.J.Clin. Pharmacol. Ther. Toxicol., 25, 97, (1987)] studied the bioavailability of amoxicillin after oral administration of controlled-release tablets, and observed that in any case, no drug was detectable after 8 hours and therefore concluded this formulation had no advantage over conventional formulation.

Uchida et. al. [Chem. Pharm. Bull., 37, 3416, (1989)] described a method for the preparation of amoxicillin microcapsules using ethyl cellulose. These microcapsules exhibited a controlled release pattern when administered to beagle dogs. However, such effect could be foreseen, since the gastric pH of the dogs which were tested is considerably higher than human gastric pH (pH of about 6 in beagle dogs, compared to pH of about 2 in humans). The preliminary studies on amoxicillin reveals that it is much less soluble at pH 6 than at pH 2 [Tsuji et.al., J. Pharm. Sci., 67, 1059 (1978)] One would expect to obtain a very quick

release of the drug from the same microcapsules if administered to humans. Hence these may not be considered to relate with the human studies.

Martin et al. (US Patent No. 5,851,550) studied the influence of co-administration of clavunic acid with amoxicillin and found that the bioavailability and subsequently therapeutic response was improved compared to conventional dosage form upon oral administration. However, the manufacture of products containing clavunic acid required controlled environmental conditions which may increase the manufacturing costs.

Hilton and Deasy [Int. J. Pharm., 86, 79, (1992)] described a floating tablet of amoxicillin trihydrate. This tablet remained buoyant for 6 hours and had satisfactory in vitro sustained release but lack of bioavailability compared to that of conventional capsule at a dose of 500mg.

Hilton and Deasy [J. Pharm. Sci., 82, 737, (1993)] also described about controlled release tablet of amoxicillin containing hydroxypropyl methylcellulose acetate succinate as a matrix carrier. This polymer retarded the release of amoxicillin in gastric pH but could not enhance its release in the duodenum, proximal parts of Jejumum of small intestine where maximum absorption is likely to take place. Further, single dose *in vivo* studies in fasting subjects showed that the tablets had a relative bioavailability of only 64.4%, probably because the poorer absorption of drug from the distal jejunum and ileum than from the duodenum and proximal jejunum.

Katzhendler (PCT application No. WO98/122091) disclosed a pharmaceutical composition for the controlled release of β-lactam antibiotics employing various types of cellulose and acrylic polymer derivatives. According to this invention, an initial release of 50.0 % drug in 3-4 hours after administration of dosage form and the drug release continued up to 8 hours. Further the author stated that the free drug is not in contact with the intestinal flora as it is embedded in a matrix and hence the drug is not degraded before it is being absorbed. These statements are contradicting with each other. As there is no carrier mediated mechanism for the absorption of β-lactams beyond the distal part of jejunum, the drug may not be absorbed completely, which may lead to reduced bioavailability and damage of gastrointestinal flora due to continuous presence of free drug in intestinal tract.

In view of the above we aimed to develop an oral extended-release preparations of different drugs belonging to β-lactam antibiotics group such as pencillins and cephalosporins to optimize therapeutic response of these drugs. A promising approach for achieving this would be optimization of the drug release such that total dose from the dosage form is released within the time of transit through absorption window. The advantages of such preparations are

(a) improving patient compliance by minimizing the frequency of drug administration to once or twice a day, and (b) avoiding the damage to the gastrointestinal flora.

The present invention is based on our finding that *invitro* dissolution profile of an antibiotic from an extended release composition containing an antibiotic or its prodrugs, coated with release modulating polymer which maintains the integrity of the dosage form in varying pH conditions of gastrointestinal tract, compressed into tablets or filled into gelatin capsules or as a dry syrup for reconstitution, when administered orally to humans for the treatment of infectious diseases provides a therapeutic concentration over an extended period of time with better patient compliance. This provides preprogrammed, unattended delivery of drug at a rate and for a time period meeting to therapeutic need. Such drug delivery system minimizes patients intervention and maximizes compliance with the prescribed dose regimen.

The present invention relates to a pharmaceutical composition in the form of an extended release oral drug delivery system comprising an active ingredient such as β-lactam antibiotic agent having a specific absorption site in gastrointestinal tract in combination with a polymeric material forming a matrix along with other pharmaceutically acceptable additives, wherein at least 25% of active antibiotic agent is released from said matrix within 0.5 to 1.0 hour after oral administration and a substantial amount of remaining active ingredient over an extended period, but within 2 to 5 hours after administration. This facilitates the complete absorption of the active ingredient before it crosses the "absorption window" where an active carrier mediated transport takes place across the g.i.t. membrane. The concept of present invention can be effectively applied to any pharmaceutical agent which has an "absorption window".

The drug granules may consist of at least one β-lactam antibiotic along with other pharmaceutically acceptable additives, a release modulating polymer with plasticizer and anti-adherent. The pharmaceutical composition of the invention can be in the form of (a) tablet containing drug granules, diluents or fillers, lubricants (b) capsule containing drug granules, fillers, lubricants or (c) dry syrup containing granules admixed with additives such as sweetners, flavours etc, suitable for oral administration upon reconstitution.

Accordingly the main objective of the present invention is to provide a novel extended release pharmaceutical composition containing antibacterial substance selected particularly from β-lactam antibiotics which are useful for the treatment of infectious diseases.

Another objective of the present invention is to provide a novel extended release pharmaceutical composition containing an antibiotic which is effective for a longer period of time when compared to the conventional immediate release pharmaceutical composition.

Still another objective of the present invention is to provide a novel pharmaceutical composition which is therapeutically effective over an extended period of at least 10 -14 hours, providing initial dose of active substance for absorption immediately i.e. within 0.5 to 1.0 hour and to release substantial amount of the remaining active substance at a rate sufficient to maintain the drug concentration in therapeutically effective range for a desired period of time.

Accordingly, the present invention provides a novel oral extended release pharmaceutical composition containing an antibiotic, useful for the treatment of infectious diseases comprising the drug in the form of a tablet or capsule or dry syrup for reconstitution made from the granules of drug coated with release modulating polymer composition. The formulation also contain necessary pharmaceutical additives.

According to another embodiment the invention also provides a process for the preparation of the above said pharmaceutical composition.

According to the present invention, an extended release pharmaceutical composition containing a β-lactam antibiotic capable of providing the required initial dose followed by

extended release of the remaining drug where in the active substance is selected from penicillins or cephalosporins.

An extended Pharmaceutical release composition wherein the said β-lactam antibiotic drug is selected from penicillins such penicillin V, penicillin G, amoxicillin, ampicillin, cloxacillin, oxacillin, nafcilin, and derivatives thereof or cephalosporins such as cefadroxil, cefixime,

cefuroxime axetil, cefadroxil, cefaclor and derivatives thereof. The amount of drug employed may range from 500.0 to 900.0mg more preferably 550.0 to 800.0 mg per gram of drug granules.

According to the invention the polymers used are selected from cellulose derivatives such as cellulose acetate phthalate, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, ethyl cellulose or methacrylic acid derivatives such as poly(methacrylic acid, methyl methacrylate) (1:1) and poly(methacrylic acid ethylacrylate) (1:1) (Eudragit L100 and Eudragit L100–55) and the like. The amount of polymer employed may range from about 20.0mg to about 400.0mg more preferably 25.0mg to 250.0mg per gram of drug granules.

The plasticizer is selected from among phthalate derivatives such as diethyl phthalate, dipropyl phthalate, dioctyl phthalate, dibutyl phthalate, or glycol derivatives such as propylene glycol, polyethylene glycols of molecular weight ranging from 200 – 6000, or triethyl citrate or triacetin or a mixture thereof, the amount of which may range from about 10.0% to about 30.0% by weight of the polymer. The anti-adherents used are selected from talc, magnesium stearate, calcium carbonate, magnesium carbonate, the amount of which may range from about 10.0% to about 30.0% by weight of the polymer.

The granular matrix is formulated as a unit dosage form of a tablet or a capsule or in the form of a dry syrup for reconstitution at the time of administration. The tablets and capsules contain pharmaceutical additives selected from diluents such as starch, lactose, microcrystalline cellulose, dicalcium phosphate or mixture thereof and lubricants such as talc, hydrogenated castor oil, magnesium stearate, stearic acid, calcium stearate, zinc stearate or a mixture thereof. The amount of diluents may range from about 20.0 to about 500.0 mg, more

preferably 50.0 to 400.0mg per gram of drug granules. The amount of lubricant may range from about 5.0 to about 50.0mg more preferably 10.0 to 40.0mg per gram of drug granules.

The dry syrup dosage units contain pharmaceutically acceptable additives selected from sweeteners such as sucrose, glucose, aspartame, sodium saccharin, N-methyl glycerrhezinate, fructose; flavours such as pineapple, strawberry, banana, vanilla, orange, mango, raspberry; colours such as titanium dioxide, erythrosine, brilliant blue, indigo carmine, tartrazine, ponceau 4R, sunset yellow, quinoline yellow, red oxide of iron, yellow oxide of iron;

preservatives such as methyl paraben, propyl paraben and their sodium salts; buffers and flavour enhancers such as citric acid, sodium citrate and the like; antioxidants such as sodium sulphite, sodium bisulphite, sodium metabisulphite, sodium benzoate, butylated hydroxy toluene, butylated hydroxy anisole and the like.

According to another embodiment the invention also provides a process for the preparation of the above said composition, which comprises

i) Preparation of granules comprising drug.

ii) Coating of the granules with a polymer dissolved in a mixture of organic solvents along with a plasticizer and anti-adherent.

iii) Formulating the granules into tablets or capsules or dry syrup for reconstitution with suitable pharmaceutical additives.

According to the above the present invention provides a method for preparing the granules by dry granulation or wet granulation employing polymer solution in an organic solvent or blend of solvents. The granules are further coated with a release modulating polymeric composition in a blend of organic solvents such as acetone, ethyl alcohol, isopropyl alcohol, methylene chloride and the like.

The granules are admixed with diluents and lubricants followed by either compression into tablets on a rotary compression machine or filled in to hard gelatin capsules on a capsule-filling machine. The dry syrup may be prepared by admixing the granules with sweeteners, flavours, colourants, preservatives, antioxidants and buffers and flavour enhancers.

The controlled yet complete release of antibiotic prior to crossing the absorption window will have maximum bioavailability with enhanced therapeutic response, minimizes local side effects, reduced dosing frequency and improved patient compliance.

The dosage form described herein provides controlled drug entry into systemic circulation via gastrointestinal tract. It has advantages over conventional dosage forms for systemic therapy. The rationale for such dosage form is based on its capability of maintaining drug concentrations in blood within a range that selectively elicits desired therapeutic effects over an extended time period in comparison to conventional dosage forms.

Advantages:

1) Prolonged therapeutic response when compared to conventional oral formulations.
2) Reduce the dosing frequency.
3) Improves patient compliance.
4) Avoids intestinal flora damage.

The invention is described in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

EXAMPLE –I

Stage 1

Composition:	**mg / g**
Ampicillin Trihydrate	900.00
Hydroxypropyl methylcellulose phthalate	60.00
Diethylphthalate	18.00
Talc	22.00
Isopropyl alcohol	qs.
Acetone	qs.

Hydroxypropyl methylcellulose was dissolved in a blend of isopropyl alcohol and acetone along with diethyl phthalate and dispersed talc in it. The compacted granules of ampicillin trihydrate were coated with the polymer composition and dried at 50°C.

Stage 2

Composition:	**mg / g**
Ampicillin coated granules	560.00
Ampicillin granules	145.00
Starch	180.00
Microcrystalline cellulose powder	95.00
Talc	10.00
Magnesium stearate	10.00

The ampicillin coated granules were mixed with ampicillin trihydrate granules, starch and microcrystalline cellulose powder and lubricated with talc and magnesium stearate. The lubricated granules were compressed into tablets on a rotary tablet press.

EXAMPLE -II

Stage 1

Composition:	**mg / g**
Cefadroxil Monohydrate	925.00
Poly(methacrylic acid, methyl methacrylate)	45.00
Triethyl citrate	14.00
Talc	16.00
Isopropyl alcohol	qs.
Acetone	qs.

Poly(methacrylic acid, methyl methacrylate) was dissolved in a blend of isopropyl alcohol and acetone along with triethyl citrate and dispersed talc in it. The compacted granules of cefadroxil monohydrate were coated with the polymer composition and dried at 50°C.

Stage 2

Composition:	**mg / g**
Cefadroxil coated granules	520.00
Cefadroxil granules	140.00
Starch	180.00
Microcrystalline cellulose powder	140.00
Magnesium stearate	20.00

The cefadroxil coated granules were mixed with cefadroxil granules, starch and microcrystalline cellulose powder and lubricated with magnesium stearate. The lubricated granules were compressed into tablets on a rotary tablet press.

EXAMPLE –III

Stage 1

Composition:	**mg / g**
Cloxacillin Sodium	800.00
Cellulose acetate phthalate	70.00
Hydroxy propyl methylcellulose	90.0
Diethylphthalate	19.50
Talc	24.00
Isopropyl alcohol	qs.
Methylene chloride	qs.

Cellulose acetate phthalate was dissolved in a blend of isopropyl alcohol and methylene chloride along with diethyl phthalate and dispersed talc in it. The compacted granules of cloxacillin sodium containing hydroxypropyl methylcellulose were coated with the polymer composition and dried at 50°C.

Stage 2

Composition:	**mg / g**
Cloxacillin coated granules	540.00
Cloxacillin Sodium granules	160.00
Starch	115.00
Dicalcium phosphate	70.00
Microcrystalline cellulose powder	95.00
Magnesium stearate	20.00

The starch, dicalcium phosphate and microcrystalline cellulose powder were mixed and granulated with starch paste. The wet mass was passed through 14# and dried at 65°C. The cloxacillin coated granules were mixed with the above dry granules along with cloxacillin sodium granules and lubricated with magnesium stearate. The lubricated granules were filled into hard gelatin capsules on a capsule-filling machine.

EXAMPLE – IV

Stage 1

Composition:	**mg / g**
Cefuroxime Axetil	920.00
Hydroxypropyl methylcellulose phthalate	54.00
Diethylphthalate	10.80
Talc	15.20
Isopropyl alcohol	qs.
Acetone	qs.

Hydroxypropyl methylcellulose was dissolved in a blend of isopropyl alcohol and acetone along with diethyl phthalate and dispersed the talc in it. The compacted granules of cefuroxime axetil were coated with the polymer composition and dried at 50°C.

Stage 2

Composition:	**mg / 15ml**
Cefuroxime coated granules	450.00
Cefuroxime axetil granules	150.00
Sodium CMC	40.50
Sodium citrate	16.00
Sodium benzoate	39.00
Quinoline Yellow	1.00
Sunset Yellow	1.50
Pineapple dry flavour	10.00
Orange DC 116 flavour	6.00
Straberry DC 109 flavour	2.60
Vanilla DC 110 flavour	2.80
Colloidal silicon dioxide	25.00
Sucrose	2500.00

Sucrose was milled to a fine grade and mixed with other ingredients which are previously sifted through 30# and finally mixed with the cefuroxime granules. The dry mixture was filled in to unit dose packs.

CLAIMS:

01) An extended pharmaceutical release composition containing at least one β-lactam antibiotic in the form of granular matrix of about 50.0% to about 90.0 % by weight, about 2.0% to about 40% of polymer by weight, 1.0% to about 20.0% of pharmaceutically acceptable inactive ingredients, the granular matrix is further coated with polymer composition comprising of a film forming polymer and other coating aids. wherein about 25% of the said active ingredient is released after 1hr of oral administration and the remainder of active ingredient is release at a controlled rate before crossing the absorption window.

02) An extended release pharmaceutical composition according to claim 1 wherein the said β-lactam antibiotic drug is selected from penicillins such penicillin V, penicillin G, amoxicillin, ampicillin, cloxacillin, oxacillin, nafcilin, and derivatives thereof or cephalosporins such as cefadroxil, cefixime, cefuroxime axetil, cefadroxil, cefaclor and derivatives thereof.

03) An extended release pharmaceutical composition of β-lactam antibiotics according to claim 1 which provides therapeutically effective concentrations of drug in blood over an extended period of 8 to 12 hours.

04) An extended release pharmaceutical composition of β-lactam antibiotics according to claim 1 wherein the granular matrix is coated with a composition from about 1.0% to about 20.0% of granular matrix weight and the polymeric composition is comprised of from about 40.0% to about 80.0% by weight of polymer and from about 10.0% to about 30.0% by weight of plasticizer and from about 10.0% to about 30.0% by weight of anti adherent.

05) An extended release pharmaceutical composition of β-lactam antibiotics according to claim 1 wherein the polymer used in preparing the granular matrix and film is selected from cellulose derivatives such as cellulose acetate phthalate, hydroxypropyl methylcellulose and hydroxypropyl methylcellulose phthalate and the like or methacrylic

acid derivatives such as poly(methacrylic acid, methyl methacrylate) (1:1) and poly(methacrylic acid, ethylacrylate) (1:1) and the like, the amount of which may range from 2% to about 40% by weight of granules.

06) An extended release pharmaceutical composition of β-lactam antibiotics according to claim 1 wherein the plasticizer used in the film coating of granular matrix is selected from diethyl phthalate, dipropyl phthalate, dioctyl phthalate, dibutyl phthalate, propylene glycol, polyethylene glycols of molecular weight ranging from 200 – 6000, triethyl citrate, triacetin or a mixture thereof, the amount of which may range from about 10.0% to about 30.0% by weight of the polymer. The antiadherants used are selected from talc, magnesium stearate, calcium carbonate, magnesium carbonate, the amount of which may range from about 10.0% to about 30.0% by weight of the polymer.

07) An extended release pharmaceutical composition of β-lactam antibiotics according to claim 1 wherein the granular matrix is formulated as a unit dosage form of a tablet or a capsule or in the form of a dry syrup for reconstitution at the time of administration.

08) An extended release pharmaceutical composition of β-lactam antibiotics according to claim 1 and 8 wherein the unit dosage form of tablet and capsule contains further pharmaceutically acceptable additives selected from diluents and disintegrants such as starch, lactose, microcrystalline cellulose and dicalcium phosphate from about 5.0% to about 50.0% by weight and lubricants selected such as talc, hydrogenated castor oil, magnesium stearate, stearic acid, calcium steareate, zinc stearate, from about 0.5% to about 4.0% by weight

09) An extended release pharmaceutical formulation of β-lactam antibiotics according to claim 1 and 8 wherein the dry syrup dosage units contain further pharmaceutically acceptable additives selected from sweeteners such as sucrose, glucose, aspartame, sodium saccharin, N-methyl glycerrhezinate, fructose; flavours such as pineapple, strawberry, banana, vanilla, orange, mango, raspberry; colours such as titanium dioxide, erythrosine, brillient blue, indigo carmine, tartrazine, ponceau 4R, sunset yellow, quinoline yellow, red oxide of iron, yellow oxide of iron; preservatives such as methyl paraben, propyl paraben and their sodium salts; buffers and flavour enhancers such as

citric acid, sodium citrate and the like; antioxidants such as sodium sulphite, sodium bisulphite, sodium metabisulphite, sodium benzoate, butylated hydroxy toluene, butylated hydroxy anisole and the like.

10) An extended release pharmaceutical formulation of β-lactam antibiotics according to claim 1 wherein the process for preparing the same, which comprises

i) Preparation of granules comprising drug.

ii) Coating of the granules with a polymer dissolved in a mixture of organic solvents along with a plasticizer and anti-adherent.

iii) Formulating the granules into tablets or capsules or dry syrup for reconstitution with suitable pharmaceutical additives.